Application No. 10/762,911
Amendment Dated December 9, 2004
Reply to Office Action of September 9, 2004

REMARKS

In the Office Action dated September 9, 2004, claims 29-38 were examined with the result that all claims were rejected. In response, Applicant submits the following remarks. In view of these remarks, reconsideration of this application is requested.

In the Office Action, claims 29-38 were rejected under the judicially created Doctrine of Obvious Type Double Patenting as being unpatentable over claims 21-35 of U.S. Patent 5,945,410 as well as claims 27-37 and 41-43 of U.S. Patent 6,127,559. The Examiner indicated that although the instant claims 29-38 are not identical with the claims in the '410 and '559 references, they are not patentably distinct from each other because the presently claimed compounds contain a methyl group at the carbon 2 position of the A-ring whereas the prior art references disclose only an alkyl group at the carbon 2 position. Further, the Examiner indicates that because the instant claims and the prior art claims are both drawn to a method of treating metabolic bone disease, it would have been obvious to one of ordinary skill in the art to prepare additional compounds useful for the treatment of metabolic bone disease because the references teach the use of vitamin D compounds for such purposes.

The Examiner indicated that a timely filed Terminal Disclaimer may be used to overcome the Obviousness Type Double Patenting rejections made in this Office Action. However, Applicant believes the presently claimed compound may be distinguished from the activities of the prior art compounds, as disclosed in the '410 and '559 references, and therefore, believes the instantly claimed compounds are not obvious in view of the prior art disclosure.

First, Applicant would like to refer to the data evidencing the biological activity of the presently claimed compound, namely, 20(S)-1α-hydroxy-2α-methyl-19-nor-vitamin D_3, which can be found in the specification as filed at pages 18-20 as well as Table 1 at page 22 and Figures 1 and 2. From these

data, it is clear that the 20(S)-2α-methyl compound claimed herein is significantly more active than 1α-25-dihydroxyvitamin D_3 in both gut calcium transport and bone calcium mobilization (serum calcium), especially at the lower dose of 130 pmols/day. Thus, it can be concluded that the 20(S)-2α-methyl compound claimed herein stimulates both activities significantly more than 1α,25-dihydroxyvitamin D_3. Therefore, it can be concluded that the 20(S)-2α-methyl compound claimed herein has significant and very potent calcemic activity. Applicant refers the Examiner specifically to page 20, lines 14-22, and the data in Table 1.

Comparing the presently claimed compound to what is disclosed in the '410 reference clearly shows that the activity of the presently claimed compound is significantly different from what is taught in the '410 reference. More specifically, Applicant refers the Examiner to the description in the '410 reference at column 15, line 59 through column 16, line 21 as well as the data in Table 1. The data for the 20(S)-2-methyl S and R mixture found in Table 1 demonstrate that this mixture of compounds, at the 260 pmol/day dose, showed only bone calcium mobilization activity being higher than 1α,25-dihydroxyvitamin D_3. The gut calcium transport data at the 260 pmol/day dose was about the same as 1α,25-dihydroxyvitamin D_3. In addition, at the 130 pmol/day dose level this mixture of compounds produced no significant change in intestinal calcium transport activity while still having strong bone calcium mobilizing activity at that dose. The activity can be summarized by the following statement found at column 16, lines 15-18:

> "These results illustrate that the 2-methyl and 20(S)-2-methyl derivatives of 19-nor-1,25-$(OH)_2D_3$ are selective for the mobilization of calcium from bone."

Thus, the '410 patent concludes that the 20(S)-2-methyl S and R mixture has bone calcium mobilization activity that is higher than 1α,25-dihydroxyvitamin

D_3 but intestinal calcium transport activity that is only the same as or less than 1α,25-dihdroxyvitamin D_3.

In contrast, as discussed above, the instantly claimed compound has significantly higher activity than 1α,25-dihydroxyvitamin D_3 in both intestinal calcium transport activity and bone calcium mobilization activity. Thus, one skilled in the art would have predicted that the instantly claimed compound would have the same or similar activities as that described and disclosed in the '410 reference, yet as discussed above, it is clear that the activities of the instantly claimed compound are unexpectedly different from the activities of the compounds described and disclosed in the '410 reference. Therefore, Applicant believes the Examiner should withdraw the obviousness type double patent rejection based upon what is disclosed in the '410 reference.

Turning now to the '559 reference utilized by the Examiner, Applicant would like to refer to the description found at column 21, lines 32-65 as well as the data in Table 3. Referring to the 2α-methyl-19-nor-20(S) compound, the data in Table 3 of the '559 reference demonstrate that this compound has intestinal calcium transport activity and bone calcium mobilization activity that is greater than 1α,25-dihydroxyvitamin D_3 at the 260 pmol/day dose. Although the instantly claimed compound has similar calcemic activity, the instantly claimed compound has significantly different activity when it comes to cell differentiation. As can be seen in Figure 4 of the '559 patent, the 2α-methyl-19-nor-20(S) compound (18) has cell differentiation activity which is greater than 1α,25-dihydroxyvitamin D_3. This is evidenced by the fact that the ED_{50} for compound (18) occurs at a lower concentration than it does for 1α,25-dihydroxyvitamin D_3. The description supports this conclusion by stating at column 23, lines 23-26 the following:

> "It was found that all of the synthesized vitamin D analogs with the unnatural 20(S)-configuration were more potent than 1α-25-$(OH)_2D_3$."

Thus, the '559 reference concludes that the 2α-methyl-19-nor-20(S) compound (18) has higher cell differentiation activity than 1α,25-dihydroxyvitamin D_3.

In contrast, Applicant refers the Examiner to Figure 2 in the present patent application wherein the cell differentiation activity of the instantly claimed compound (1a) is demonstrated as being lower than 1α,25-dihydroxyvitamin D_3. The ED_{50} for the instant compound (1a) is about one order of magnitude less active than 1α,25-dihydroxyvitamin D_3. As can be seen from Figure 4 in the '559 reference, the ED_{50} for the prior art 2α-methyl-19-nor-20(S) compound (18) is about two orders of magnitude greater than 1α,25-dihydroxyvitamin D_3. Therefore, the difference in cell differentiation activity is about three orders of magnitude. Clearly, such activity would not be predicted based upon what is described and taught in the '559 reference. One skilled in the art would predict that the compounds should have approximately the same cell differentiation activity, but instead it is clear that the instantly claimed compound has much lower cell differentiation activity than its prior art compound (18). As a result, Applicant believes the Examiner should withdraw the obviousness type double patenting rejection based upon what is taught in the '559 reference.

An effort has been made to place this application in condition for allowance and such action is earnestly requested.

Respectfully submitted,
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